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GENETIC DISORDERS – DEVELOPMENT

Albuminuria in nondiabetic relatives of IDDM patients with and without diabetic nephropathy

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Background. In non–insulin-dependent diabetes mellitus (NIDDM), there is a clustering of an elevated urinary albumin excretion rate (U-AER) in nondiabetic relatives of albuminuric patients. Whether this is also the case in insulin-dependent diabetes mellitus (IDDM) is unknown.

Methods. Overnight U-AER was measured in 186 nondiabetic first-degree relatives of 80 IDDM patients with diabetic nephropathy (U-AER > 200 μg/min or 300 mg/24 hours; DN+) and in 52 relatives of 25 IDDM patients without nephropathy (U-AER < 20 μg/min; DN−). The two groups of relatives were comparable regarding gender distribution, age, obesity, blood pressure, prevalence of antihypertensive therapy, and smoking habits.

Results. No difference was found in overnight U-AER between relatives of patients with DN+ and DN− [median (range), 3.4 (0.1 to 372) vs. 4.0 (0.2 to 62) μg/min, respectively, P = NS]. The proportion of relatives with a U-AER = 10 μg/min was 12% in DN+ compared with 8% in DN− (P = NS). Among relatives of DN+, those with antihypertensive treatment (AHT+) had higher U-AER compared with those without [AHT+ vs. AHT−, 5.0 (0.5 to 372) vs. 3.4 (0.1 to 26.5) μg/min, $P < 0.01$], a phenomenon that was not seen among relatives of DN−[AHT + vs. AHT−, 3.6 (2.1 to 24.3) vs. 4.0 (0.2 to 61.5) μg/min, P = NS]. However, this analysis was impaired by the small number of relatives of DN− with hypertension (N = 7).

Conclusions. In IDDM, we found no clustering of elevated U-AER in nondiabetic relatives of patients with nephropathy. This is different from what has been reported in NIDDM, and suggests heterogeneity in the genesis of albuminuria in diabetes.

Diabetic nephropathy is characterized by persistent albuminuria, an elevation of arterial blood pressure, a relentless decline in renal function, and increased cardiovascular morbidity and mortality. This late complication of diabetes occurs in 10 to 40% of patients with insulin-dependent diabetes mellitus (IDDM) [1, 2].

Genetic factors have been proposed to play a role in the development of diabetic nephropathy. For instance, familial predisposition to hypertension [3–5], non–insulin-dependent diabetes mellitus (NIDDM) [6, 7], and cardiovascular disease [8] have all been implicated to increase the risk of diabetic nephropathy. Furthermore, albuminuria has been found to cluster in siblings concordant for IDDM [9–11] and NIDDM [12–14].

Interestingly, nondiabetic first-degree relatives of albuminuric patients with NIDDM have been found to have an elevated urinary albumin excretion rate (U-AER) compared with relatives of normoalbuminuric NIDDM patients [13, 15–17]. Therefore, in NIDDM, minor abnormalities of U-AER seem to be present even in the absence of diabetes in individuals with a potential genetic susceptibility to diabetic nephropathy. The question of whether a similar elevation of U-AER is also present in nondiabetic relatives of IDDM patients with diabetic nephropathy has not been addressed. Therefore, the aim of the present study was to assess U-AER in nondiabetic first-degree relatives of IDDM patients with and without diabetic nephropathy.

METHODS

Subjects

A family study dealing with genetic factors in the genesis of diabetic nephropathy was initiated in 1994 at the Helsinki University Central Hospital. The recruitment of the IDDM patients with and without nephropathy has been presented in detail elsewhere [6]. In short, the family study consists of first-degree relatives of 137 IDDM patients with diabetic nephropathy (U-AER > 200 μg/min or 300 mg/24 hours in two of three consecutive urine collections; DN+) attending the renal outpatient clinic or the dialysis unit of Helsinki University Central Hospi-

Key words: insulin-dependent diabetes mellitus, heredity, urinary albumin, arterial blood pressure, progressive renal disease, diabetic nephropathies.

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Table 1. Recruitment of relatives

	DN+		DN−	
	All	Parents/siblings	All	Parents/siblings
Total number of relatives	386	171/215	102	52/50
Alive	313	117/196	87	44/43
Contacted	247	105/142	63	36/27
Attending	231	104/127	58	35/23
Nondiabetic	209	88/121	57	34/23
U-AER available	186	77/109	52	30/22

Data are presented as number of relatives at each step.

Table 2. Characteristics of IDDM patients with (DN+) and without (DN−) diabetic nephropathy

Variable	DN+	DN−	*P*
N	80	25	—
Male/female	52/28	8/17	<0.01
Age *years*	41 ± 1	41 ± 2	NS
Duration of diabetes *years*	30 ± 1	27 ± 2	NS
BMI, male patients kg/m^2	24.6 ± 0.5	24.3 ± 0.7	NS
BMI, female patients kg/m^2	23.6 ± 0.6	23.6 ± 0.7	NS
WHR, *male patients*	0.92 ± 0.01	0.85 ± 0.02	<0.05
WHR, *female patients*	0.84 ± 0.01	0.80 ± 0.02	<0.01
Smoking %	33	20	NS
History of retinal photocoagulation %	91	28	<0.001
Systolic blood pressure *mm Hg*	155 ± 2	128 ± 3	<0.001
Diastolic blood pressure *mm Hg*	87 ± 1	77 ± 2	<0.001
HbA1c %	8.8 ± 0.2	8.1 ± 0.2	<0.05
Serum creatinine *μmol/L*	177 (68–1176)	78 (57–101)	<0.001
U-AER[a] *μg/min*	928 (70–8936)	4 (1–11)	—
ESRD %	51	—	—

Abbreviations are: BMI, body mass index; WHR, waist/hip ratio; U-AER, urinary albumin excretion rate; and ESRD, end-stage renal disease. Data are presented as mean ± SEM or median (range).

[a]Not measured in patients with ESRD

tal and of 54 patients with a normal albumin excretion rate (U-AER < 20 μg/min in three overnight urine collections; DN−) recruited from either the diabetic outpatient clinic from the same hospital or the local Diabetes Association. In total, we studied 450 first-degree relatives of these 191 type I diabetic patients. To assess U-AER in the relatives, a timed overnight urine collection was introduced as a part of the study protocol from November 1, 1995. The study protocol was approved by the local ethical committee, and a written informed consent was obtained from all participating subjects.

The recruitment of the relatives is listed in Table 1. The characteristics of the IDDM patients and their nondiabetic first-degree relatives are presented in Tables 2 and 3, respectively. A medical history regarding medication, smoking habits, and treatment for diabetes, cardiovascular disease, and hypertension was obtained from the relatives. None of the relatives studied had a history of diabetes or of any renal disorder. A timed overnight urine collection was performed for measurement of U-AER and blood samples drawn for determination of HbA1c, cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and creatinine. Six of the studied relatives (4 fathers and 2 mothers of patients with nephropathy) had a serum creatinine slightly exceeding the reference value of our laboratory. Exclusion of these six relatives had no effect on the results. Blood pressure (Korotkoff I-V) was measured with a calibrated mercury sphygmomanometer, with the subject in sitting position after a five-minute rest. The mean value of two recordings was used in analysis. Body weight and height were measured in indoor clothing. Waist circumference was measured midway between the iliac crest and the lowest rib, and hip circumference was measured at the widest part of the gluteal region, and the waist/hip ratio (WHR) was calculated. Smoking was defined as regular smoking of at least one daily cigarette, cigar, or pipe during the year before participation in the study.

Laboratory tests

The urinary albumin concentration was determined by radioimmunoassay (albumin-RIA; Pharmacia, Uppsala, Sweden) with a coefficient of variation of 4%. Serum cholesterol (normal range, 3.6 to 7.0 mmol/L), HDL-cholesterol (normal range, women 1.10 to 2.35 and men 0.95 to 2.00 mmol/L) and triglycerides (normal range, 0.4 to 1.7 mmol/L) were all measured on a Hitachi 917 automated analyzer with enzymatic colorimetric tests.

Table 3. Characteristics of nondiabetic first-degree relatives of IDDM patients with (DN+) and without (DN−) diabetic nephropathy

Variable	DN+	DN−	*P*
N	186	52	—
Male/female	85/101	22/30	NS
Age *years*	52 ± 1	54 ± 2	NS
BMI kg/m^2	26.4 ± 0.3	26.0 ± 0.6	NS
WHR	0.88 ± 0.01	0.86 ± 0.01	<0.05
Systolic blood pressure *mm Hg*	138 ± 2	138 ± 3	NS
Diastolic blood pressure *mm Hg*	84 ± 1	84 ± 2	NS
Antihypertensive medication %	17	13	NS
Smoking %	27	25	NS
HbA1c %	5.52 ± 0.03	5.54 ± 0.06	NS
Serum cholesterol *mmol/L*	5.25 ± 0.08	5.63 ± 0.15	<0.05
Serum HDL-cholesterol *mmol/L*	1.47 ± 0.03	1.47 ± 0.05	NS
Serum triglycerides *mmol/L*	1.31 ± 0.06	1.26 ± 0.09	NS
Serum creatinine *μmol/L*	80 (44–128)	80 (57–112)	NS

Glycosylated hemoglobin was measured by high-pressure liquid chromatography (normal range, 4.0 to 6.0%) and serum creatinine by a kinetic Jaffé method (normal range, women 50 to 110 and men 55 to 115 mmol/L). Urine and serum samples were stored at −20°C prior to determination.

Statistical analysis

The significance of difference in categorical variables between the groups was tested with the chi-squared test. The significance of difference in continuous variables was tested using the Student's *t*-test (normally distributed) and with the Mann–Whitney *U*-test (non-normally distributed). A two-tailed *P* value of less than 0.05 was considered statistically significant. Continuous variables are presented as mean ± SEM or median (range).

RESULTS

Table 1 depicts the recruitment of the first-degree relatives of the IDDM patients presented in Table 2. The proportion of parents alive was lower among parents of DN+ patients compared with parents of DN− patients (68 vs. 84%, respectively, $P < 0.05$). No difference was present in the proportion of living siblings between the two groups. There were no significant differences in the proportions of living relatives that were contacted or contacted relatives that attended. Among the attending relatives, there was an excess of diabetes in relatives of patients with DN+ (10 vs. 2%, respectively, $P = 0.05$).

The two groups of relatives were comparable regarding gender distribution, age, body mass index, blood pressure, and prevalence of antihypertensive therapy and smoking (Table 3). As depicted in Figure 1, overnight U-AER did not differ between relatives of patients with and without diabetic nephropathy [DN+, 3.4 (0.1 to 372) vs. DN−, 4.0 (0.2 to 62), P = NS]. The proportion of relatives with a U-AER · 10 μg/min was 12% in DN+ compared with 8% in DN− (P = NS). Stratified analyses in male [DN+ vs. DN−, 3.4 (0.1 to 372) vs. 4.2 (1.1 to 24.3) μg/min, P = NS] and in female relatives [DN+ vs. DN−, 3.5 (0.2 to 118) vs. 3.5 (0.2 to 61.5) μg/min, P = NS] as well as in parents [DN+ vs. DN−, 3.5 (0.1 to 372) vs. 4.0 (0.2 to 61.5) μg/min, P = NS] and siblings [DN+ vs. DN−, 3.4 (0.2 to 118) vs. 3.6 (0.4 to 14.4) μg/min, P = NS] revealed no differences in U-AER between the two groups of relatives.

Of the relatives of patients with DN+, 32 (17%) relatives were treated for hypertension, while the corresponding number in relatives of DN− was 7 (13%, P = NS). Among the relatives of DN+, those with antihypertensive treatment (AHT) had higher U-AER compared with those without [5.0 (0.5 to 372) vs. 3.4 (0.1 to 26.5) μg/min, $P < 0.01$]. A similar phenomenon was not seen among relatives of DN−, where U-AER was comparable in relatives with and without treatment for hypertension [AHT+ vs. AHT−, 3.6 (2.1 to 24.3) vs. 4.0 (0.2 to 61.5) μg/min, P = NS].

To assess for a possible effect of impaired survival among relatives of patients with nephropathy, the relatives were further divided into tertiles according to age (Fig. 2). The tertiles corresponded to an age below 43 years (tertile I), between 43 and 62 years (tertile II), and above 62 years (tertile III). No difference in U-AER was observed in any of the tertiles.

To control for the varying number of relatives studied per diabetic patient, we randomly selected one relative per diabetic patient. In this analysis, no difference in U-AER was observed between the two groups [DN+ (N = 80) vs. DN− (N = 25), 3.6 (0.1 to 168) vs. 3.6 (0.2 to 61.5) μg/min, P = NS].

DISCUSSION

In this study, we found no difference in U-AER between nondiabetic first-degree relatives of IDDM patients with and without diabetic nephropathy.

Studies in both IDDM [9–11] and NIDDM [12–14] have reported a familial clustering of U-AER in siblings with diabetes. In addition, a recent study reported not only a familial clustering of albuminuria, but also a strong concordance in the severity and pattern of glomerular lesions in IDDM sibling pairs [18]. Therefore, in the presence of the diabetic milieu, genetic factors seem to influence U-AER and, at least in IDDM, renal structural changes.

Several family studies in NIDDM have consistently reported elevated U-AER in nondiabetic first-degree relatives of NIDDM patients with microalbuminuria or macroalbuminuria when compared with relatives of normoalbuminuric patients [13, 15–17]. Therefore, abnormalities of U-AER seem to be present even in the absence of diabetes in individuals with a potential genetic predisposition to diabetic nephropathy. However, diabetes is

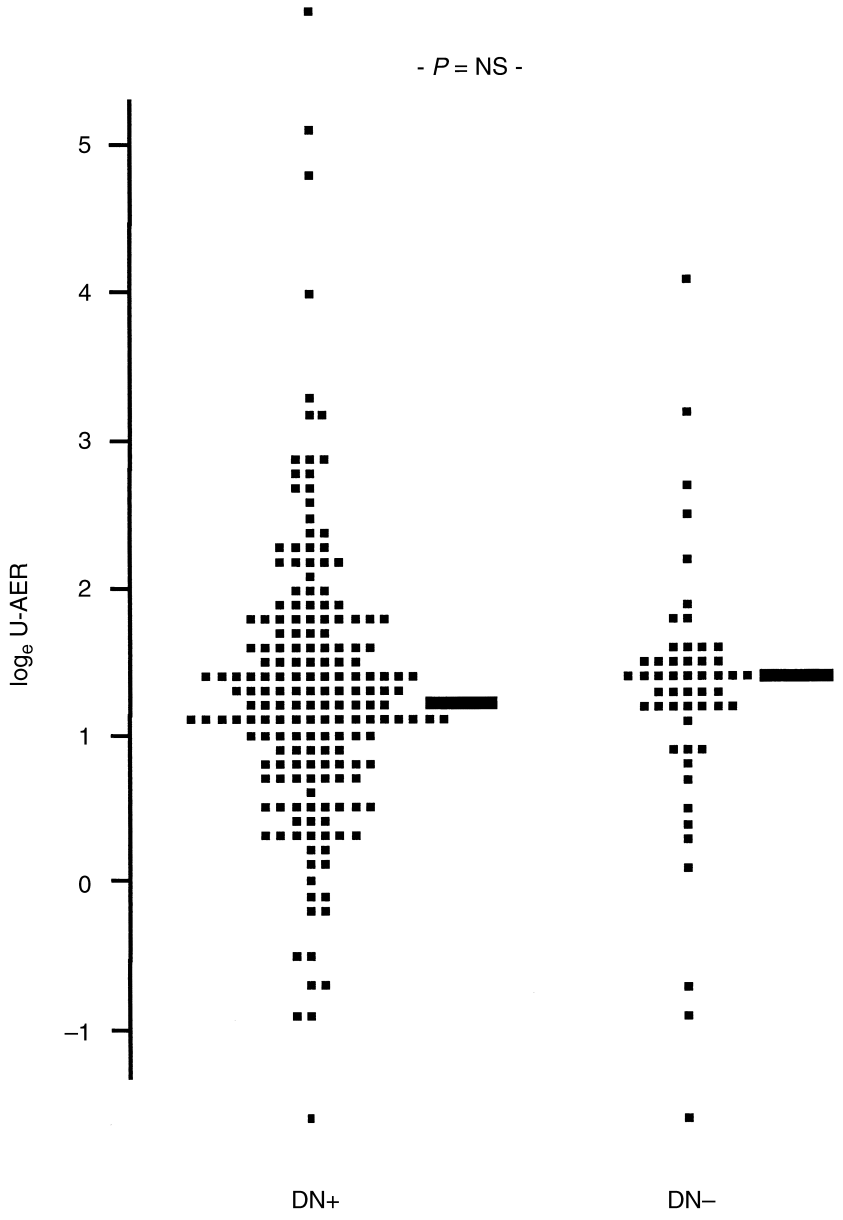

Fig. 1. Logarithmically transformed urinary albumin excretion rate (log U-AER) in relatives of patients with (DN+) and without diabetic nephropathy (DN−). The horizontal lines represent median values.

a heterogenous and complex disease entity [19], and it may be that elevation of U-AER is also caused by etiological mechanisms of heterogeneous nature. Our finding of a lack of similar clustering of elevated U-AER in first-degree relatives discordant for IDDM is an interesting and new support of this view.

Since there was no difference in U-AER between relatives of patients with and without nephropathy, the power of the study to detect such a difference is of crucial importance. According to a power calculation, our study would have detected a difference between the groups of 0.45 in the mean value of the logarithmically transformed U-AER. In other words, since the median value for U-AER was 4.0 μg/min in the control group, we can, under the assumption that the distributions of U-AER in the two groups are unchanged, exclude a median value of 5.1 μg/min or more in the relatives of patients with nephropathy. The studies performed in NIDDM [13, 15, 16] have reported clearly elevated (approximately two times higher) U-AER in nondiabetic relatives of patients with nephropathy compared with relatives of patients without nephropathy. A recent study in relatives of Finnish NIDDM patients found this difference to be somewhat smaller [17]. Although our study cannot totally exclude a minimal elevation of U-AER in nondiabetic relatives of IDDM patients with nephropathy, such an elevation is substantially smaller than what on average has been reported in NIDDM. It seems justified to question the

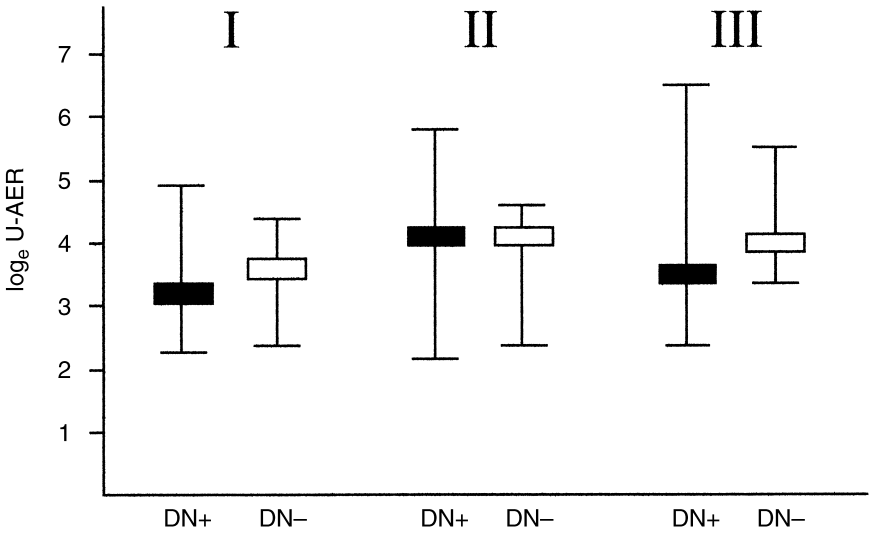

Fig. 2. Log U-AER in relatives of patients with (DN+) and without diabetic nephropathy (DN−) divided into age tertiles. Data are presented as median and 25th and 75th percentiles. There was no difference in U-AER between relatives of DN+ and DN− in any of the tertiles.

pathophysiological or biological relevance of an elevation of U-AER in nondiabetic relatives of patients with diabetic nephropathy not detected by our sample size.

Among relatives of patients with nephropathy, relatives with hypertension had higher U-AER than those without. A similar effect was not seen among relatives of patients without nephropathy. It is very tempting to interpret this as supportive of a familial clustering to elevated U-AER that becomes obvious only in the presence of an unmasking factor, in this case hypertension. However, because of the small number of relatives with hypertension in the control group, such conclusions cannot be drawn on the basis of our study. It is evident, however, that this hypothesis should be tested.

In contrast to our previous findings [4], the prevalence of hypertension was similar in the two groups of relatives. In part, this could be due to the use of insensitive methods, since we applied 24-hour ambulatory blood pressure monitoring in our previous article [4]. Another explanation may lie in the fact that the relatives were on average 14 years younger in the present study, mostly because of the inclusion of not only parents, but also siblings. Analyses more powerful than simple comparisons of prevalence numbers, for instance, cumulative incidence rates [4], were not appropriate in the present study because of the small number of relatives with hypertension in the control group. In addition, we have confirmed an excess of parental hypertension in patients with nephropathy in the entire set of families recruited at our hospital thus far [6], of which the present study constitutes a subgroup. We can therefore not totally exclude a selection bias of an unknown nature to have occurred despite our attempts to minimize such a possibility. The absence of a clustering of hypertension in relatives of patients with nephropathy in the present study may therefore have several explanations.

Elevated U-AER is associated with an increased risk for cardiovascular morbidity and mortality [20, 21] and is more prevalent in conditions such as diabetes [22], hypertension [23], and insulin resistance [24]. These features have all been found to cluster in family members of IDDM patients with diabetic nephropathy [3, 4, 6, 8, 25, 26]. Therefore, since we studied U-AER in surviving nondiabetic relatives, the influence of the selection procedure on our results must be carefully evaluated. Regarding survival, we found an excess of mortality among parents of patients with nephropathy. To test for an effect of selective mortality on our results, we divided the relatives into tertiles according to their age. If there would exist a clustering of elevated U-AER in nondiabetic relatives of patients with nephropathy that is masked by an impaired survival in this group, one would expect this elevated U-AER to be discernible in the younger relatives still unaffected by the effects of selective mortality. Our analysis showed no tendency toward such a difference. Furthermore, diabetes was more common among relatives of patients with nephropathy, in line with what we have reported previously [6]. However, among the siblings, in whom the prevalence of diabetes was still very low because of their age distribution, no difference in U-AER was observed. Taken together, although we found no clear indications of a selection bias to have occurred, it is still possible that an underestimation of the "true" U-AER in relatives of IDDM patients with nephropathy may have taken place.

It is therefore of utmost importance to compare our results with those of the previous studies performed in NIDDM. Gruden et al found that offspring of NIDDM patients with microalbuminuria or macroalbuminuria had elevated U-AER compared with offspring of normoalbuminuric patients [15]. The study was performed as a case-control study with 20 offspring in each group,

all of whom were normotensive, had normal glucose tolerance, and normal creatinine clearance. This observation was confirmed by Strojek et al, who found elevated overnight and exercise-induced U-AER in 26 offspring of NIDDM patients with microalbuminuria and macroalbuminuria compared with 30 offspring of patients with normoalbuminuria [16]. Again, the studied offspring were selected to be normotensive and to have normal oral glucose tolerance. Family studies from Italy [13] and Finland [17] extended the finding to nondiabetic siblings of NIDDM patients. In line with observations in IDDM, elevated U-AER in NIDDM has been associated with a familial predisposition to hypertension [5] and diabetes [7]. Furthermore, elevated U-AER is associated with an increased mortality rate [20], which could have caused an effect of selective mortality in the studies on siblings of NIDDM patients [13, 17]. In other words, it seems justified to assume that the studies in NIDDM were affected by a similar possibility of selection bias as our study. The most likely explanation for the discrepancy between our and the previous studies, therefore, is that a true difference in the mechanisms regulating U-AER in nondiabetic relatives of IDDM and NIDDM patients exists.

How can this difference between IDDM and NIDDM be explained? One scenario could be that a common susceptibility to elevated U-AER exists in both IDDM and NIDDM, but that an additional trigger is needed for the susceptibility to manifest as an increased U-AER. Individuals with a family history of NIDDM display various metabolic and hemodynamic alterations already in the prediabetic state [27, 28]. A family history of IDDM confers an increased risk of IDDM [29] but, to our knowledge, has no consequences that would affect U-AER in the nondiabetic state. It could be hypothesized that such a trigger, for instance a slightly impaired insulin sensitivity, elevated blood pressure or some other related phenomenon, is present in the nondiabetic relatives of NIDDM patients, but not in those of IDDM patients. The findings that persistently elevated U-AER often is present at diagnosis [30] and even precedes development of NIDDM [31], while usually is absent at diagnosis of IDDM [32], is compatible with this explanation. On the other hand, our results may also reflect differences in the susceptibility to elevated U-AER in IDDM and NIDDM. In support of this view, only 30% of NIDDM patients with microalbuminuria (comparable to the cases included in the previous studies [13, 15, 16]) have been found to have a morphology typical of diabetic nephropathy [33]. IDDM patients with overt nephropathy (comparable to our cases) have a morphologically rather monotonous pattern typical of diabetic nephropathy [34]. Furthermore, microalbuminuria is a strong predictor of overt diabetic nephropathy in IDDM [35], while in NIDDM, microalbuminuria is prognostic of cardiovascular events rather than of overt nephropathy [36]. Our results may therefore be a consequence of differences in the mechanisms behind, and perhaps also in the genetic susceptibility to, elevated U-AER between IDDM and NIDDM.

In conclusion, we found no difference in U-AER between nondiabetic first-degree relatives of IDDM patients with and without diabetic nephropathy. This is different from what has consistently been reported in NIDDM, and suggests heterogeneity in the genesis of albuminuria in diabetes.

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